The Epithelial-Mesenchymal Transcription Factor SNAI1 Represses Transcription of the Tumor Suppressor miRNA let-7 in Cancer.

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Public Summary:
We aimed to determine the mechanism of epithelial-mesenchymal transition (EMT)-induced stemness in cancer cells. Cancer relapse and metastasis are caused by rare stem-like cells within tumors. Studies of stem cell reprogramming have linked let-7 repression and acquisition of stemness with the EMT factor, SNAI1. The mechanisms for the loss of let-7 in cancer cells are incompletely understood. In four carcinoma cell lines from breast cancer, pancreatic cancer, and ovarian cancer and in ovarian cancer patient-derived cells, we analyzed stem cell phenotype and tumor growth via mRNA, miRNA, and protein expression, spheroid formation, and growth in patient-derived xenografts. We show that treatment with EMT-promoting growth factors or SNAI1 overexpression increased stemness and reduced let-7 expression, while SNAI1 knockdown reduced stemness and restored let-7 expression. Rescue experiments demonstrate that the pro-stemness effects of SNAI1 are mediated via let-7. In vivo, nanoparticle-delivered siRNA successfully knocked down SNAI1 in orthotopic patient-derived xenografts, accompanied by reduced stemness and increased let-7 expression, and reduced tumor burden. Chromatin immunoprecipitation demonstrated that SNAI1 binds the promoters of various let-7 family members, and luciferase assays revealed that SNAI1 represses let-7 transcription. In conclusion, the SNAI1/let-7 axis is an important component of stemness pathways in cancer cells, and this study provides a rationale for future work examining this axis as a potential target for cancer stem cell-specific therapies.

Scientific Abstract:
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